(FILE 'HCAPLUS' ENTERED AT 11:41:05 ON 12 MAY 2004)
L1   132367 SEA FILE=HCAPLUS ABB=ON PLU=ON (ARRAY OR APPARAT? OR
                DEVICE OR EQUIPMENT) AND (WELL OR WELLED OR PARTITION?)
L2   12672 SEA FILE=HCAPLUS ABB=ON PLU=ON L1 AND (CRYSTAL? OR
                RECRYSTAL? OR PRECIPITAT?)
L3   468 SEA FILE=HCAPLUS ABB=ON PLU=ON L2 AND SOLVENT
L4   7 SEA FILE=HCAPLUS ABB=ON PLU=ON L3 AND (BP(S)BOIL? OR
                BOIL?(W)(PT OR POINT))
L5   5 SEA FILE=HCAPLUS ABB=ON PLU=ON L4 AND (ACID OR BASE OR
                AMINE OR SALT)
L6   5 SEA FILE=HCAPLUS ABB=ON PLU=ON L5 AND (METHOD OR
                TECHNIQUE)
L7   3 SEA FILE=HCAPLUS ABB=ON PLU=ON L6 AND (PHARMACEUT? OR
                COMPOSITION OR DRUG OR FORMULAT?)

L7   ANSWER 1 OF 3 HCAPLUS COPYRIGHT 2004 ACS on STN   ← Same as L81 Ans. 2-20
ED   Entered STN: 21 Feb 2003
ACCESSION NUMBER: 2003:133581 HCAPLUS
DOCUMENT NUMBER: 138:180672
TITLE: **Apparatuses** and **methods** for
                          creating and testing pre-**formulations**
                          and systems for same
INVENTOR(S):   Carlson, Eric D.; Cong, Peijun; Chandler,
                          William H., Jr.; Chau, Henry K.; Danielson,
                          Earl; Desrosiers, Peter J.; Doolan, Robert D.;
                          Wu, Luping
PATENT ASSIGNEE(S):   Symyx Technologies, Inc., USA
SOURCE: PCT Int. Appl., 229 pp.
                          CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

        PATENT NO.   KIND DATE   APPLICATION NO. DATE
        ---------------   ---- --------   --------------- --------
        WO 2003014732   A1   20030220   WO 2002-US16962 20020524
            W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH,
                CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD,
                GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ,
                LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ,
                NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ,
                TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM,
                AZ, BY, KG, KZ, MD, RU, TJ, TM
            RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE,
                CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT,
                SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE,
                SN, TD, TG
        US 2003116497   A1   20030626   US 2002-156245 20020524
        US 2003119060   A1   20030626   US 2002-156295 20020524
        US 2003118078   A1   20030626   US 2002-156329 20020524
        US 2003124028   A1   20030703   US 2002-156222 20020524
PRIORITY APPLN. INFO.:   US 2001-311332P P 20010810
AB   The invention provides **methods, apparatus,** and
     systems for performing high-throughput preparation and screening of
     salts and polymorphs of **drug** candidates. The

                    Searcher :   Shears   571-272-2528

invention is directed towards enhancing the pre-**formulation**
discovery process used for **drug** development. In
particular, processes that determine suitable **salts** and
processes that discover substantially every polymorph that can form
from a particular **drug** candidate are provided. The
processes are performed using several **apparatuses** that are
specifically configured to carry-out various steps in a
high-throughput characterization process. One such **apparatus**
is configured for synthesizing a plurality of library members based
on, for example, a library model generated by a computer system.

REFERENCE COUNT: 7   THERE ARE 7 CITED REFERENCES AVAILABLE FOR
                                THIS RECORD. ALL CITATIONS AVAILABLE IN
                                THE RE FORMAT

L7   ANSWER 2 OF 3 HCAPLUS   COPYRIGHT 2004 ACS on STN
ED   Entered STN: 16 Dec 2001   ← *same as L81 Ans. 18-20*
ACCESSION NUMBER: 1908:11195 HCAPLUS
DOCUMENT NUMBER: 2:11195
ORIGINAL REFERENCE NO.:   2:2482f-i,2483a-i
TITLE: Contribution to the Knowledge of Gelatinization
                           Processes, I and II
AUTHOR(S):   Levites, S. Ya.
CORPORATE SOURCE: Chem. Lab. Kaiserl, Inst. f. Expt. Med, St.
                           Petersburg
SOURCE: Zeitschrift fuer Chemie und Industrie der
                           Kolloide (1908), 2, 208-15,237-41
                           CODEN: ZCIKAL; ISSN: 0372-820X
DOCUMENT TYPE: Journal
LANGUAGE: Unavailable
AB   (1) Certain factors influence the condition of a dissolved
     substance. The same material may be dissolved as a
     crystalloid in one **solvent** and as a colloid in
     another, e. g., **salts** of the higher fatty **acids**
     dissolve in water as colloids and in alcohol as **crystalloids**
     . The concentration of the solution has a similar influence,
     substances such as sodium palmitate and sodium silicate acting as
     crystalloids in dilute solution and as colloids in more
     concentrated solutions. According to many the colloidal solution is
     not a true solution in the sense of the present solution theory, but
     is a pseudo-solution, the dissolved body being in the form of small
     submicroscopic particles. As far as conformation to the laws of
     boiling and freezing points is concerned, colloids form only
     pseudo-solutions. If, however, we define solution as a simple
     homogeneous mixture, the **composition** of which can be
     varied within certain limits, then we have a definition not
     dependent on the state of aggregation, and a colloidal solution
     would come under this definition. The gelatinization process is not
     a sudden change from liquid to jelly, but proceeds with greater or
     less velocity, depending on the nature of the solution and other
     conditions. No sharp line can be drawn as in the change from liquid
     to solid phases. The gradual change is **well** indicated by
     the gradual change of the viscosity of the solution. Observations
     on the viscosity of gelatinizing colloidal solutions, and on
     non-gelatinizing solutions of glutin, agar-agar, alkaline casein
     solution, and water solutions of albumin and commercial peptone,
     made with the Ostwald **apparatus** and calculated according

to the equation n = ts/tlsl where l is the time the unknown solution
takes to run out, s its specific gravity, and llSl the same for
water, are recorded. The influence of concentration and
temperature, and of foreign substances, on the viscosity of
colloidal solutions was first studied. The viscosity increases with
increased concentration. In concentrated solutions the Arrhenius
formula, n = Ax where A is a constant and x the concentration of the
solution, agrees with the experimental observations, but in more
dilute solutions (0.5-1.5%) the linear equation n = 1 + an shows
best agreement. Glutin heated in a closed flask for some time at
the **boiling point** of water loses its capacity to
gelatinize, and if it be **precipitated** from the solution
with alcohol and ether, an amorphous mass results which is readily
soluble in water, called P-glutin. Such P-glutin shows a lower
viscosity than ordinary glutin. A rise of temperature decreases the
viscosity of a solution and a lowering of temperature increases it,
but gelatinizing colloidal solutions show a constant value only
under definite temperature conditions. For a colloidal solution of
definite concentration there is a temperature minimum below which
the viscosity gradually increases till gelatinization takes place.
The viscosity is assumed to be constant if inside of three hours it
changes not more than 0.15-0.20%. The viscosity of a solution can
remain constant only when there is one homogeneous liquid phase;
when a second solid phase appears the homogeneity is destroyed and
the viscosity ceases to be constant. The increase in viscosity is
proportional to the rate of formation of the solid phase. The
method of studying the influence of foreign bodies on the
viscosity was as follows: to study the effect of N KI solution on
1.5% glutin solution 25 cc. of a 3% glutin solution are mixed with
25 cc. of a 2N KI solution, all solutions being at the same
temperature. Tabulated results show that all materials which
decrease the viscosity of water also decrease the viscosity of the
colloidal solution, and all which increase the viscosity of water
also increase the viscosity of the colloidal solution. This rule
holds for very different organic colloids so long as there is no
chemical action of the foreign body. NaNO3 is an exception, causing
a decrease where one would expect an increase in the viscosity of
agar-agar solution. The results on gelatinizing solutions are the
same provided we are dealing with one homogeneous phase. The nature
of the **crystalloid** admixture has an influence on the
temperature minimum at which the viscosity is constant, some
decreasing it while others raise it. The effect of the introduction
of a **crystalloid** into a solution of another
crystalloid has been studied by Rudorf (Z. physik.Chemical,
1903, 43) who finds cases analogous to the colloid and
crystalloid mixtures. The influence of the
crystalloid is independent of the number of colloids in the
solution. Egg albumin and Witte-peptone conduct themselves the same
as glutin. If the mixture contains more than one
crystalloid or if there is a chemical action of the colloid
and **crystalloid** then the rule does not hold. Different
salts added to alkaline casein solution give a mixture with
a viscosity differing widely from the added viscosities of the two
solutions. All inorganic **salts** used decreased the
viscosity of the casein solution, while sodium **salts** of
acetic, salicylie, and benzoic **acids** gave variable

LANGUAGE: Japanese
STATUS: New

AB   New artificial receptors based on calix¢5!arene for
      Buckminsterfullerene and neutral guest molecules are reported.
      Calix¢5!arene derivatives form inclusion complexes with C60 in
      a variety of organic **solvents** such as toluene, benzene,
      CS2, and o-dichlorobenzene. The association constants of the
      complexes were determined by using Benesi-**Hildebrand**
      method. The structure of the complex in the solid state was
      disclosed by X-ray **crystallography**. 13C signal of C60 in
      the presence of the host molecule exhibits 0.35ppm up-field shifts.
      This result indicates that C60 bound within the cavity of the host
      molecule. "Upper rim" functionalized calix¢5!arene having two
      benzoic **acid** moieties is synthesized. The host molecule
      binds neutral guests, such as 9-ethyladenine, 2-aminopyrimidine, and
      imidazole, by the use of hydrogen bonding interaction. The
      association constants were determined by 1H-NMR titration using a
      non-linear least squares method. The structures of the complexes
      were predicted by molecular mechanics calculation using MacroModel
      V. 4.5. (author abst.)

L93 ANSWER 5 OF 6 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS
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ACCESSION NUMBER: 84021476 EMBASE
DOCUMENT NUMBER: 1984021476
TITLE: Isocratic chromatographic retention data for
                     estimating aqueous solubilities of acidic, basic and
                     neutral drugs.
AUTHOR: Hafkenscheid T.L.; Tomlinson E.
CORPORATE SOURCE: Physical Pharmacy Group, Department of Pharmacy,
                     University of Amsterdam, 1018 TV Amsterdam,
                     Netherlands
SOURCE: International Journal of Pharmaceutics, (1983) 17/1
                     (1-21).
                     CODEN: IJPHDE
COUNTRY: Netherlands
DOCUMENT TYPE: Journal
FILE SEGMENT: 037   Drug Literature Index
                     030   Pharmacology
LANGUAGE: English

AB   For 108 compounds of diverse chemical character (including drug
      molecules) isocratic reversed-phase liquid chromatographic retention
      parameters have been used in modifications of the **Hildebrand**
      -Scott equation to estimate compound acqueous solubility. The
      relationships found are valid for both liquids are
      crystalline solids, as well as for stronger (pK(a) > 6.5)
      bases that are chromatographed in a partially ionized state. It is
      observed that there is a significant constant difference in
      behaviour between **acid** and alcohol molecules and neutral
      and base molecules. This difference can be empirically corrected for
      during solubility estimations. Comparison of the use of
      octan-1-ol/water distribution coefficients in these equations shows
      that the use of isocratic chromatographic retention parameters lead
      to significantly better estimations of compound aqueous solubility.

L93 ANSWER 6 OF 6   MEDLINE on STN

                Searcher :   Shears   571-272-2528

AB   A method is suggested to obtain solubility parameters for
     crystalline solid compounds involving a quadratic equation
     based on the original Scatchard-**Hildebrand** solubility
     expression. The geometric mean delta 1 delta 2, of the
     Hildebrand approach is replaced by w12 = K delta 1 delta 2,
     and log alpha 2/(V2 phi 2(2)/2.3RT) is regressed against delta 1 in
     a second-degree power series for parabens and benzoic **acid**
     in a series of normal alcohols. The method provides reasonable
     solubility parameters for the solid solutes and affords a convenient
     calculation of the solubility of drugs in a homologous series of
     solvents.

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results. The influence of the **crystalloid** is dependent on the anion. (II). See following abstract.

L7   ANSWER 3 OF 3   HCAPLUS   COPYRIGHT 2004 ACS on STN
ED   Entered STN: 16 Dec 2001   *← Same as L81 Ans. 20-20*
ACCESSION NUMBER: 1907:1700   HCAPLUS
DOCUMENT NUMBER: 1:1700
ORIGINAL REFERENCE NO.:   1:437g-i,438a-i,439a-i,440a-i,441a-d
TITLE: A **Method** for the Separation and
                          Determination of Chlorophyl Derivatives
AUTHOR(S):   Willstatter, Richard; Mieg, Walter
CORPORATE SOURCE: Chem. Lab., Konigl. Akad. Wissenschaften,
                          Munchen
SOURCE: Ann. (1907), 350, 1-47
DOCUMENT TYPE: Journal
LANGUAGE: Unavailable

AB   The author's **base** their **method** upon the peculiar
     basic nature of many chlorophyl derivatives and apply it to two
     series of compounds, the one comprising products obtained by the
     action of alkali on a chlorophyl extract and derivatives obtained
     from them by the action of **acids,** the second consisting of
     products obtained principally from alkachlorophyl by treatment with
     alcoholic hydro-chloric **acid.**   The first form olive-green
     to green solutions in indifferent **solvents,** blue-green to
     green solutions with **acids.**   The second show similar color
     in **acid** solutions, but in neutral solutions are a
     brilliant red.   The series are named respectively the phytochlorines
     and the phytorhodines and the individual members designated
     provisionally phytochlorine a, phytochlorine b, etc.   The
     phytochlorines and phytorhodines are insoluble in water, more or
     less soluble in organic **solvents.**   As weak **acids**
     they dissolve in alkalies and may be completely extracted from ether
     solution even by ammonium hydroxide or sodium bicarbonate.   They
     contain no phenolic hydroxyl and but a single esterifiable
     acid group.   Their esters are insoluble in alkalies.   All
     are weak **bases** whose **salts** are completely
     decomposed by water.   Unlike the **acid** properties, however,
     the basic properties show differences and gradations, differing from
     any yet described in connection with weak organic **bases.**
     To extract these substances from ether solution by means of
     hydrochloric **acid** it is necessary to use **acid** of
     a definite minimum concentration and by treating the ether solution
     of a mixture of the phytochlorines, for example, successively with
     hydrochloric **acid** solutions of increasing concentration it
     is possible to effect a very satisfactory separation and eventual
     purification of the individual members of the series.   The following
     tables illustrate the differences in solubility upon which the
     separation **methods** are based: Traces go into solution in
     hydrochloric **acid** of,Dissolved very freely in hydrochloric
     acid of,Dissolved almost completely in hydrochloric
     acid of;Phytochlorine a...............,3.5%,6.5%,7.5%;",
     b...............,1.5%,3.5%,5.0%;",c...............,0.5%,1.5%,2.0%;
     ",d...............,0.15%,0.5%,1.0% On shaking ether solutions of
     phytochlorines a and b with equal volumes of hydrochloric
     acid of varying concentration the following results were
     obtained: Phytochlorine,Hydrochloric **acid** of,Percentage of

substance dissolved;a............................,8.0%
,84.1;a.................................,7.0%,73.8;
a....................................,6.0%,60.7;
b....................................,5.5%,74.4;
b....................................,4.0%,54.7;
b....................................,2.5%,26.4 The colors of the
various solutions and extracts give useful indications of the
quality and quantity of the substances present. Four closely
related phytochlorines of differing basicity, but exhibiting similar
colors in neutral, **acid** and alkaline solutions were
obtained. The more strongly basic members show fluorescence as
well as more pronounced color. The solubility in many
solvents, e. g., alcohol and benzene, decreases with the
increase in basic properties. All are unstable toward oxidizing and
reducing agents, and are very easily changed by heat, apparently
with loss of water. The phytorhodines, of which five (two in impure
condition) were obtained from a somewhat similar series, differ from
the phytochlorines principally in giving red instead of green
solutions in ether. It proved difficult to prepare the substances
for analysis and the empirical formulas could not be established
with certainty. The analytical results, however, point to close
similarity in **composition.** Some of the compounds seem to
be isomers, as phytochlorines a and b, phytorhodine a and
phytochlorine d, etc. Others, as phytochlorines a and d, seem to
differ by the elements of a molecule of water. The authors
interpret their analytical results provisionally by assuming three
atoms of nitrogen present in the molecules of all of these
chlorophyl derivatives and thus arrive at the following formulas for
the more important members of the series: Phytochlorine a
....,$C_{23}H_{33}O_6N_3$;",b
....,$C_{28}H_{33}O_6N_3$;",c
....,$C_{28}H_{33}O_6N_3$;",d
....,$C_{23}H_{33}O_6N_3$;Phytorhodine a
...., $C_{25}H_{33}O_6N_3$;Ethyl ester of
phytorhodine a ....,$C_{30}H_{37}O_6N_3$;Phytorhodine
b ....,$C_{28}H_{33}O_4N_3$;Ethyl ester
of phytorhodine b ....,$C_{30}H_{37}O_4N_3$ Attempts
to determine the molecular weights of the compounds by the
boiling point method were fruitless, but
an analysis of the cesium **salt** of phytochlorine b gave a
result not inconsistent with the above assumption. The new
compounds do not correspond to any of the chlorophyl derivatives
hitherto reported. While phytochlorines a and b are very similar to
E. Schunk's phyllotaonine [Pr. Roy Society, 44, 448 (1888), and 55, 351
(1894); Ann., 278, 329 (1894)] and certain of the phytorhodines
resemble the phylloporphyrine of E. Schunk and L. Marchlewski [Pr.
Roy. Society, 57, 314 (1895); Ann., 284, 81 (1894)], even a close
relationship between these, to say nothing of their identity, is
excluded by a comparison of the results of their analyses.
EXPERIMENTAL RESULTS. The chlorophyl extracts from which the
phytochlorines were obtained were prepared by boiling dried nettle
leaves with alcohol or ethyl acetate in a stone-ware extraction
apparatus and were found to contain relatively little
unchanged chlorophyl. Portions of the extract were boiled under a
reflux **apparatus** with ten parts of a 2% solution of
potassium hydroxide in 95% alcohol and, after cooling the mixture,

diluting **well** with water and neutralizing with
hydrochloric **acid,** the reaction products were extracted
with ether. The longer the digestion with alcoholic potassium
hydroxide solution continues, the more phytochlorine b and the less
phytochlorine a are obtained, owing to the conversion of the latter
into the former by the continued action of the alcoholic potash. A
digestion of about fifteen minutes gives the best relative yield of
phytochlorine a. The ether extract of the reaction products is
shaken with 17% hydrochloric **acid** whereby phytochlorines a
and b are separated from indifferent and less basic substances. The
phytochlorines are recovered by neutralizing the hydrochloric
acid solution and again extracting with ether. On shaking
this second ether extract with 3% hydrochloric **acid,**
phytochlorine b passes into solution in the hydrochloric
acid accompanied by only traces of phytochlorine a. (For
full details of the **method** of separation and purification
reference must be made to the original). Phytochlorine a
crystallizes from benzene, ether or alcohol in rosettes of
fine hard needles of bluish black color and metallic lustre which m.
with partial alteration at 181-182°. The results of the
analysis agree fairly **well** with the formula, $C_{26}H_{18}O_6N_3$.
Drying the preparation in a toluene bath or long continued heating
with **solvents** causes the loss of half a molecule of water
which is restored on again shaking with ether and water. The
dehydrated preparation m. above 200°. Solutions of
phytochlorine a in ether and in alcohol show olive-green color and
moderately strong red fluorescence. In glacial acetic **acid**
solution the color is a brilliant blue accompanied by strong red
fluorescence. Phytochlorine a possesses weakly basic and marked
acid properties. It is almost completely extracted from
ether solution by 8% hydrochloric **acid,** scarcely at all by
3% **acid.** The hydrochloric **acid** solutions are
deep bluish green, appearing red by transmitted light, but show no
fluorescence. Alkaline solutions, even sodium bicarbonate, extract
phytochlorine a completely from its ether solution. The resulting
solutions are olive-brown and without fluorescence. Boiling
phytochlorine a with a methyl alcohol solution of hydrogen chloride
converts it apparently into an ester. Oxidizing and reducing agents
decolorize it. Digestion with alcoholic potash converts it
completely into phytochlorine b. Phytochlorine b shows the same
colors and fluorescence in indifferent **solvents** as
phytochlorine a, but its acetic **acid** solution is light
violet-blue. It forms bluish black **crystals** with metallic
lustre which m. with decomposition at 183-190°. Analysis
points to the same formula as for phytochlorine a. It shows the
same behavior toward alkalies but is more basic than phytochlorine
a, being partially extracted from ether solution by even 2%
hydrochloric **acid** and almost completely by 5%. A cesium
salt containing 21.8% cesium was prepared, but did not seem
to be a pure primary **salt.** Hence, no definite conclusions
regarding the molecular weight could be drawn from its
composition. By boiling phytochlorine b with a concentrated
solution of hydrogen chloride in methyl alcohol a compound without
acid properties was obtained in the form of steel-blue
crystals which underwent no change on heating in the toluene
bath and m. fairly sharply at 140°. The results of the

analysis were consistent with the assumption that the compound was a
methyl ester of phytochlorine b formed with simultaneous loss of one
molecule of water between two molecules of the phytochlorine
[=(C28H24O4.8N3)2]. From this an **acid** saponification
product was obtained having the properties of phytochlorine b. The
ester was less basic than the phytochlorine. Phytochlorines a and b
on standing with concentrated hydrochloric **acid** generally
go over into a series of new compounds which differ from the above
described phytochlorines in the more markedly green color of their
ether and the blue color of their hydrochloric **acid**
solutions. Of these only the two most basic, phytochlorines c and
d, are described. They were separated by fractionation with 0.5%
and 1.5% hydrochloric **acid**. Phytochlorine c is readily
extracted from ether by 2% hydrochloric **acid**. It
dissolves in dilute alkalies with a green, in dilute **acids**
with a blue color, both solutions showing red fluorescence. The
preparations showed no definite melting points. Analysis makes the
formula, C23H14O8N3, probable. Phytochlorine d is characterized by
the most brilliant colors. It is the strongest **base** and
the weakest **acid** of the series. It differs from the other
phytochlorines in dissolving in water, the resulting violet solution
showing strong red fluorescence. This water-soluble form, however,
seems to exist only in the absence of **acids**. From its
solutions in alkalies, after large dilution with water, it may be
extracted by ether, while 1% hydrochloric **acid** extracts it
very completely from its ether solution. The hydrochloric
acid solution is strongly fluorescent. The dry substance is
readily subject to change on heating and even on standing and so has
no definite m. p. and could not be prepared for analysis in its
original form. The analysis of a long dried preparation indicated
the formula, C28H23O6N3. Preparation of the Phytorhodines. From an
alcoholic extract of unchanged chlorophyl prepared without heating
two alkachlorophyls were obtained, the first by
precipitation with potassium hydroxide and filtering, the
second from the filtrate by **precipitation** with alcoholic
calcium chloride solution. On heating with alcoholic hydrochloric
acid these alkachlorophyls yielded two closely related but
different series of phytorhodines. From the potassium compound were
obtained by extraction with ether, treatment with dilute alkali and
fractionation by hydrochloric **acid** of graded
concentration, phytorhodine a (together with two similar but
stronger **bases**), the ester of phytorhodine a, and
phytorhodine d, insoluble in ether. From the calcium
alkachlorophyl, phytorhodine b, its ester, a stronger **base**
, phytorhodine c and phytorhodine e, insoluble in ether, were
similarly obtained. The yields throughout were very small.
Phytorhodine a in indifferent **solvents** shows a carmine-red
color with little fluorescence, in hydrochloric **acid**
solution bluish green with slight red fluorescence. It requires
7.5% hydrochloric **acid** for its complete extraction from
ether. M. indefinitely between 130°-140°. Analysis
indicates the formula, C28H23O6N2. The ethyl ester of phytorhodine
a, insoluble in alkalies but more weakly basic than phytorhodine a,
requires 9.5% hydrochloric **acid** for its extraction from
ether. Alcoholic potash or hydrochloric **acid** saponifies
it, regenerating phytochlorine a. The **acid** solution of

the ester is violet-green with slight red fluorescence, the ether
solution brilliant carmine and more strongly fluorescent. Its
crystals liquefy under 100° without showing a sharp
m. p. Analysis indicates the formula, $C28H25O6N3$. Phytorhodine b
shows purple-red color and fluorescence in ether solution,
violet-blue with red fluorescence in **acid**. It is a weaker
base than phytorhodine a, requiring 9% hydrochloric
acid for its extraction from ether. It **crystallizes**
well but has no sharp m. p. Very dilute sodium hydroxide
precipitates brown flocks from its ether solution. Analyses
leads to the formula, $C28H25O6N3$. Its ethyl ester shows the same
colors in solutions, but is less basic. It **crystallizes**
well, but m. with decomposition at 76-80°. Analysis
points to $C30H37O4N3$. Phytorhodine b may be regenerated from it by
saponification. Phytorhodine c is much more strongly basic than the
b compound, but shows similar colors in solution. It is accompanied
in the reaction product by a still stronger and very highly colored
base. The authors regard the analysis as indicating the
formula, $C34H26O9N6$. Phytorhodines d and e, weakly basic and
insoluble in ether, accompany a and b, respectively. The
hydrochloric **acid** solution of the former shows a
changeable violet-green color, that of the latter a changeable
violet-blue, both with fluorescence. The analyses indicate
$(C28H26O5.5N3)2$ for d and $C28H31O4N3$ for e. Phytorhodine f
accompanies phytochlorines a and b and is separated from the ether
solution after their extraction, but displays the characteristic
colors of the phytorhodines. The results of the analysis lie
between $C28H26O6N3$ and $C28H29O4N3$. The compound is stable toward
alcoholic potash and toward strong hydrochloric **acid**.
Complex Compounds with **Salts**. The phytochlorines and the
phytorhodines both form two series of double compounds with metallic
acetates, one set in each case being insoluble in ether, the other
soluble. The copper and the zinc compounds are very intensely
colored. The ether solutions of the zinc double **salts**
fluoresce strongly. The zinc **salts** are dissolved and
decomposed into their constituents by 10-20% hydrochloric
acid, but the copper **salts** require concentrated
acid for their solution and then are not decomposed.

(FILE 'MEDLINE, BIOSIS, EMBASE, WPIDS, CONFSCI, SCISEARCH,
JICST-EPLUS, JAPIO, PASCAL, FEDRIP, DISSABS' ENTERED AT 11:44:11 ON
12 MAY 2004)

L8   1 S L7 ← Same as L83 Ans. 8 - 26

L8   ANSWER 1 OF 1   WPIDS   COPYRIGHT 2004 THOMSON DERWENT on STN
ACCESSION NUMBER: 2002-750607 [81]   WPIDS
DOC. NO. NON-CPI: N2002-591116
DOC. NO. CPI: C2002-212774
TITLE: New determination **method** of
                         multicomponent chemical **composition**(s)
                         comprises selecting experimental parameters,
                         causing **apparatus** to conduct experiments,
                         and selecting multicomponent chemical
                         compositions of matter based on results.
DERWENT CLASS: B04 C07 D14 J04 T01
INVENTOR(S):   CHIN, D; LEVINSON, D A

Searcher :   Shears   571-272-2528

PATENT ASSIGNEE(S):   (CHIN-I) CHIN D; (LEVI-I) LEVINSON D A; (TRAN-N)
                        TRANSFORM PHARM INC
COUNTRY COUNT: 101
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2002077772	A2	20021003	(200281)*	EN	62

    RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC
        MW MZ NL OA PT SD SE SL SZ TR TZ UG ZM ZW
    W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ
      DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP
      KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ
      NO NZ OM PH PL PT RO RU SD SE SG SI SK SL TJ TM TN TR TT TZ
      UA UG UZ VN YU ZA ZM ZW

PATENT NO	KIND	DATE	WEEK	LA	PG
US 2002177167	A1	20021128	(200281)		
EP 1381857	A2	20040121	(200410)	EN	

    R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK
      NL PT RO SE SI TR

APPLICATION DETAILS:

PATENT NO	KIND		APPLICATION	DATE
WO 2002077772	A2		WO 2002-US9274	20020325
US 2002177167	A1	Provisional	US 2001-278401P	20010323
			US 2002-103983	20020322
EP 1381857	A2		EP 2002-733893	20020325
			WO 2002-US9274	20020325

FILING DETAILS:

PATENT NO	KIND		PATENT NO
EP 1381857	A2	Based on	WO 2002077772

PRIORITY APPLN. INFO: US 2001-278401P   20010323; US
                      2002-103983   20020322
AN   2002-750607 [81]   WPIDS
AB   WO 200277772 A UPAB: 20021216
     NOVELTY - New **method** for determining multicomponent
     chemical **composition**(s) comprises:
          (1) selecting a combination of experimental parameters that may
     be varied by a high-throughput automated experimentation
     apparatus;
          (2) causing the **apparatus** to conduct experiments for
     each combinations of value(s) of the experimental parameters; and
          (3) selecting multicomponent chemical **compositions** of
     matter based on results.
          DETAILED DESCRIPTION - New **method** for the
     determination of multicomponent chemical **composition**(s)
     comprises:
          (a) selecting a combination of experimental parameters that may
     be varied by a high-throughput automated experimentation
     apparatus;
          (b) determining a first distinct combinations of value(s) of

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the experimental parameters, each combination corresponding to a distinct experiment;

(c) causing the automated experimentation **apparatus** to conduct a first set of experiments for each of at least a portion of the first distinct combinations of value(s) of the experimental parameters;

(d) determining a first collection of experimental results of the first set of experiments, the first collection comprising individual result sets, each individual result set corresponding to a distinct experiment;

(e) based on the first collection of experimental results, determining a second distinct combinations of value(s) of the experimental parameters, each combination corresponds to a distinct experiment;

(f) causing the automated experimentation **apparatus** to conduct a second set of experiments for each of at least a portion of the second distinct combinations of value(s) of the experimental parameters;

(g) determining a second collection of experimental results of the second set of experiments, the second collection comprising individual result sets, each individual result set corresponding to a distinct experiment; and

(h) selecting multicomponent chemical **compositions** of matter based on the first collection of experimental results and the second collection of experimental results.

INDEPENDENT CLAIMS are also included for:

(A) a **method** of estimating one or more properties of a multicomponent chemical **composition** comprising:

(1) receiving signals representing an experimental result set for each of the experiments conducted by a high-throughput automated experimentation **apparatus;**

(2) generating a predictive model based on signals characterizing each experimental result set according to the property to be estimated and signals characterizing the experiment with respect to a set of molecular descriptors; and

(3) estimating the property for a multicomponent chemical **composition** by providing signals characterizing the multicomponent chemical **composition** with respect to the molecular descriptors as input to the predictive model;

(B) a system for determining a multicomponent chemical **composition** comprising:

(1) a database comprising table(s) comprising molecular descriptors, compound identifiers, compound/descriptor relations associating portion(s) of the compound identifiers with molecular descriptors, empirically determined physical, chemical and biological parameters, compound/parameter relations associating compound identifier(s) with empirically determined physical, chemical and/or biological parameters, data presenting results from experiments performed with a high-throughput automated experimentation **apparatus;**

(2) a query system for selecting subsets of related information from table(s);

(3) a multidimensional representation generation module capable of generating visual representations of data sets having at least 4 dimensions; and

(4) modeling modules, each module is capable of receiving

information selected by the query system and estimating at least one property of a **formulation**;

(C) a **method** of producing **crystals**
comprising:

(1) electronically calculating a set of predicted **crystal** polymorphs of a target compound;

(2) electronically calculating expected experimental results for at least a portion of the predicted polymorphs;

(3) conducting a first **crystallization** experiments using a high-throughput automated experimentation **apparatus**; and

(4) electronically comparing at least a portion of the expected experimental results with the actual experimental results to determine which of the portion of the polymorphs were produced;

(D) a **method** for determining a solid form of a compound comprising:

(1) predicting a crystal structure of a target chemical species;

(2) selecting a first range of conditions for crystal generation;

(3) conducting a first experiments within the first range of conditions using a high-throughput automated experimentation apparatus;

(4) testing at least a portion of the experimental results of the presence of crystals;

(5) classifying at least a portion of the experiments based on predicted crystal forms;

(6) selecting a second range of conditions for crystal generation based on the classification(s); and

(7) conducting second experiments within the second range of conditions using the high-throughput automated experimentation apparatus; and

(E) a method for preparing a crystal comprising:

(1) performing simulated hydrogen-bond-biased simulated annealing to predict polymorphs of a target compound;

(2) calculating expected properties of at least one portion of the predicted polymorphs;

(3) conducting crystallization experiments using a high throughput automated experimentation apparatus;

(4) comparing measured properties of crystals produced by the crystallization experiments with the expected properties of at least a portion of the predicted polymorphs to determine which of the portion(s) of the predicted polymorphs were produced by the experiments;

(5) generating a predictive model of the relationship between experimental parameters and polymorphs produced; and

(6) calculating a set of experimental parameters for a second set of crystallization experiments from the predictive model.

USE - For determining multicomponent chemical composition(s).

ADVANTAGE - The inventive method systematically integrate all available information in a manner that permits the useful deployment of a limited number of experiments to increase or maximize the probability of yielding compounds, compositions or formulations that posses a desired property or set of properties over an expected range of conditions of manufacture, storage, administration and/or use.

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